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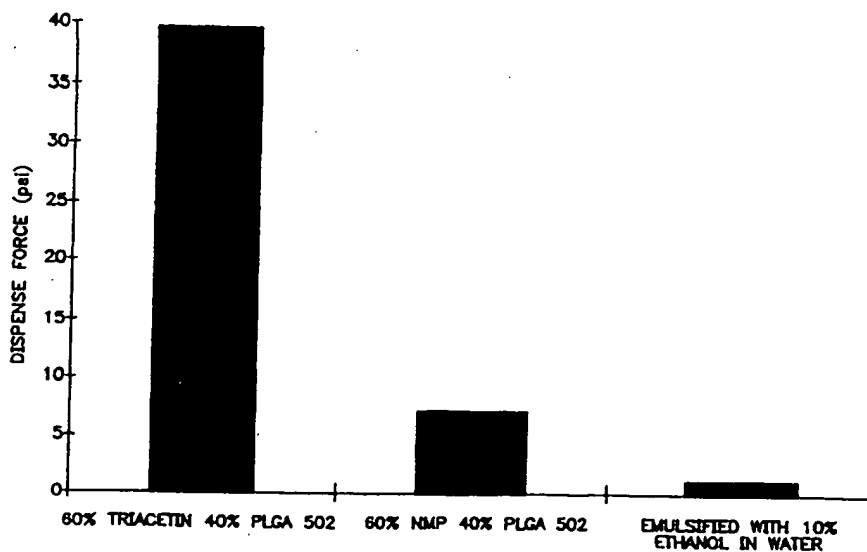
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(54) Title: INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF PREPARING THE COMPOSITION



(57) Abstract

An injectable depot gel composition containing a polymer, a solvent that can dissolve the polymer and thereby form a viscous gel, a beneficial agent; and an emulsifying agent in the form of a dispersed droplet phase in the viscous gel. The injectable depot gel composition can be prepared by mixing the polymer and the solvent so that the solvent dissolves the polymer and forms a viscous gel. The beneficial agent is dissolved or dispersed in the viscous gel and the emulsifying agent is mixed with the beneficial agent containing viscous gel. The emulsifying agent forms a dispersed droplet phase in the viscous gel to provide the injectable depot gel composition. The injectable depot gel composition can deliver a beneficial agent to a human or animal with a desired release profile.

1 **INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF**
2 **PREPARING THE COMPOSITION**
3

4

5 **BACKGROUND OF THE INVENTION**
6

7 **Field of the Invention**
8

9 The present invention relates to a depot gel composition that can be injected
10 into a desired location and which can provide sustained release of a beneficial agent.

11 The present invention also relates to a method of preparing the composition.
12

13 **Description of the Related Art**
14

15 Biodegradable polymers have been used for many years in medical
16 applications. Illustrative devices composed of the biodegradable polymers include
17 sutures, surgical clips, staples, implants, and drug delivery systems. The majority
18 of these biodegradable polymers have been based upon glycoside, lactide,
19 caprolactone, and copolymers thereof.

20 The biodegradable polymers can be thermoplastic materials which means
21 that they can be heated and formed into various shapes such as fibers, clips, staples,
22 pins, films, etc. Alternatively, they can be thermosetting materials formed by
23 crosslinking reactions which lead to high-molecular-weight materials that do not
24 melt or form flowable liquids at high temperatures.

25 Although thermoplastic and thermosetting biodegradable polymers have
26 many useful biomedical applications, there are several important limitations to their
27 use in the bodies of various animals including humans, animals, birds, fish, and

1 One way to avoid the incision needed to implant drug delivery systems is to
2 inject them as small particles, microspheres, or microcapsules. For example, U.S.
3 Patent No. 5,019,400 describes the preparation of controlled release microspheres
4 via a very low temperature casting process. These materials may or may not
5 contain a drug which can be released into the body. Although these materials can
6 be injected into the body with a syringe, they do not always satisfy the demand for a
7 biodegradable implant. Because they are particulate in nature, they do not form a
8 continuous film or solid implant with the structural integrity needed for certain
9 prostheses. When inserted into certain body cavities such as a mouth, a periodontal
10 pocket, the eye, or the vagina where there is considerable fluid flow, these small
11 particles, microspheres, or microcapsules are poorly retained because of their small
12 size and discontinuous nature. Further, the particles tend to aggregate and thus their
13 behavior is hard to predict. In addition, microspheres or microcapsules prepared
14 from these polymers and containing drugs for release into the body are sometimes
15 difficult to produce on a large scale, and their storage and injection characteristics
16 present problems. Furthermore, one other major limitation of the microcapsule or
17 small-particle system is their lack of reversibility without extensive surgical
18 intervention. That is, if there are complications after they have been injected, it is
19 considerably more difficult to remove them from the body than with solid implants.
20 A still further limitation on microparticles or microcapsulation is the difficulty in
21 encapsulating protein and DNA-based drugs without degradation caused by solvents
22 and temperature extremes.

23 The art has developed various drug delivery systems in response to the
24 aforementioned challenges. For instance, U.S. Patent No. 4,938,763 and its
25 divisional U.S. Patent No. 5,278,201 relate to a biodegradable polymer for use in
26 providing syringeable, in-situ forming, solid biodegradable implants for animals. In
27 one embodiment, a thermoplastic system is used wherein a non-reactive polymer is
28 dissolved in a biocompatible solvent to form a liquid which is placed in the animal
29 wherein the solvent dissipates to produce the solid implant. Alternatively, a

SUMMARY OF THE INVENTION

3 The present invention is a significant advance in the art and in one aspect
4 provides an injectable depot gel composition comprising:

- 5 A) a biocompatible polymer;
6 B) a solvent that dissolves the polymer and forms a viscous gel;
7 C) a beneficial agent; and
8 D) an emulsifying agent in the form of a dispersed droplet phase in the
9 viscous gel.

10 In a further aspect, the present invention provides a method of preparing an
11 injectable depot gel composition comprising:

- 12 A) mixing a biocompatible polymer and a solvent whereby the solvent
13 dissolves the polymer and forms a viscous gel;
14 B) dispersing or dissolving a beneficial agent in the viscous gel to form a
15 beneficial agent containing gel; and
16 C) mixing an emulsifying agent with the beneficial agent containing gel,
17 said emulsifying agent forming a dispersed droplet phase in the beneficial agent
18 containing gel so as to provide the injectable depot gel composition.

19 In another aspect, the present invention provides a method of preparing an
20 injectable depot gel composition comprising:

- 21 A) mixing a biocompatible polymer and a solvent whereby the solvent
22 dissolves the polymer and forms a viscous gel;
- 23 B) dispersing or dissolving a beneficial agent in an emulsifying agent to
24 form a beneficial agent containing emulsifying agent; and
- 25 C) mixing the beneficial agent containing emulsifying agent with the viscous
26 gel, said beneficial agent containing emulsifying agent forming a dispersed droplet
27 phase in the viscous gel to provide the injectable depot gel composition.

1 DESCRIPTION OF THE PREFERRED EMBODIMENTS

2
3 As explained above, one aspect of the present invention relates to an
4 injectable depot gel composition comprising:

5 A) a biocompatible polymer;

6 B) a solvent that dissolves the biocompatible polymer and forms a viscous
7 gel;

8 C) a beneficial agent; and

9 D) an emulsifying agent in the form of a dispersed droplet phase in the
10 viscous gel.

11 The polymer, solvent and emulsifying agents of the invention must be
12 biocompatible, that is they must not cause irritation or necrosis in the environment
13 of use. The environment of use is a fluid environment and may comprise a
14 subcutaneous or intramuscular portion or body cavity of a human or animal.

15 Polymers that may be useful in the invention may be biodegradable and may
16 include, but are not limited to polylactides, polyglycolides, polycaprolactones,
17 polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters,
18 polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates,
19 polyphosphazenes, succinates, poly(malic acid), poly(amino acids),
20 polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan,
21 and copolymers, terpolymers and mixtures thereof.

22 The polymer may be a polylactide, that is, a lactic acid-based polymer that
23 can be based solely on lactic acid or can be a copolymer based on lactic acid and
24 glycolic acid which may include small amounts of other comonomers that do not
25 substantially affect the advantageous results which can be achieved in accordance
26 with the present invention. As used herein, the term "lactic acid" includes the
27 isomers L-lactic acid, D-lactic acid, DL-lactic acid and lactide while the term
28 "glycolic acid" includes glycolide. The polymer may have a monomer ratio of
29 lactic acid/glycolic acid of from about 100:0 to about 15:85, preferably from about

1 polymer dissolution which leads to greater gel viscosities, with attendant higher
2 force needed to dispense the viscous gel when compared with other solvents. These
3 characteristics enable the beneficial agent to be maintained without exhibiting a
4 burst effect, but make it difficult to dispense the gel through a needle. For instance,
5 as shown in Figure 1, a gel prepared from 40% by weight of a 50:50 lactic
6 acid:glycolic polymer and 60% by weight of triacetin required about 40 psig to
7 dispense the gel through a standard 20 gauge needle at 2 cc/min while a gel
8 prepared from the same amount of polymer with 60% by weight of N-methyl-2-
9 pyrrolidone required only about 8 psig. Figure 1 further shows that when the
10 emulsifying agent (in this case 33% by weight of a 10% ethanol solution) is added
11 to the viscous gel according to the invention, the dispense force needed is only
12 about 2 psig. The shear thinning characteristics of the depot gel compositions of the
13 present invention allow them be readily injected into an animal including humans
14 using standard gauge needles without requiring undue dispensing pressure.

15 The solvent is typically present in an amount of from about 95 to about 20%
16 by weight and is preferably present in an amount of from about 80 to about 50% by
17 weight and often 65 to 55% by weight of the viscous gel, that is the combined
18 amounts of the polymer and the solvent. The viscous gel formed by mixing the
19 polymer and the solvent typically exhibits a viscosity of from about 1,000 to about
20 200,000 poise, preferably from about 5 to about 50,000 poise measured at a 1.0 sec⁻¹
21 shear rate and 25° C using a Haake Viscometer at about 1-2 days after mixing is
22 completed. Mixing the polymer with the solvent can be achieved with conventional
23 low shear equipment such as a Ross double planetary mixer for from about 1 to
24 about 2 hours.

25 The beneficial agent can be any physiologically or pharmacologically active
26 substance or substances optionally in combination with pharmaceutically acceptable
27 carriers and additional ingredients such as antioxidants, stabilizing agents,
28 permeation enhancers, etc. that do not substantially adversely affect the
29 advantageous results that can be attained by the present invention. The beneficial

1 phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole,
2 erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate,
3 dexamethasone and its derivatives such as betamethasone, triamcinolone,
4 methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl
5 ether, prednisolone, 17 α -hydroxyprogesterone acetate, 19-nor-progesterone,
6 norgestrel, norethindrone, norethisterone, norethiedrone, progesterone,
7 norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen,
8 sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol,
9 atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine,
10 methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen,
11 ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate,
12 vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz,
13 hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin,
14 alclofenac, m \acute{e} fenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine,
15 nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine,
16 lisinopril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine,
17 sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam,
18 amitriptyline, and imipramine. Further examples are proteins and peptides which
19 include, but are not limited to, bone morphogenic proteins, insulin, colchicine,
20 glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones,
21 calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating
22 hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine
23 somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, somatostatin,
24 lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and
25 antagonists, leuprolide, interferons, interleukins, growth hormones such as human
26 growth hormone, bovine growth hormone and porcine growth hormone, fertility
27 inhibitors such as the prostaglandins, fertility promoters, growth factors, coagulation
28 factors, human pancreas hormone releasing factor, analogs and derivatives of these

1 profile that depends more on the degradation of the polymer than the diffusion of
2 the beneficial agent from the composition or vice versa. In this respect, at lower
3 beneficial agent loading rates, one generally obtains a release profile reflecting
4 degradation of the polymer wherein the release rate increases with time. At higher
5 loading rates, one generally obtains a release profile caused by diffusion of the
6 beneficial agent wherein the release rate decreases with time. At intermediate
7 loading rates, one obtains combined release profiles so that if desired, a
8 substantially constant release rate can be attained. While the particular release rate
9 depends on the particular circumstances, such as the beneficial agent to be
10 administered, release rates on the order of from about 1 to about 10 micrograms/day
11 for periods of from about 7 to about 90 days can be obtained. Further, the dose of
12 beneficial agent may be adjusted by adjusting the amount of injectable depot gel
13 injected. As will be apparent from the following results, one can avoid a burst
14 effect and administer on the order of 1% by weight of the beneficial agent in the
15 composition during the first day.

16 Figure 2 shows the release rates obtained from the compositions described
17 with regard to Figure 1. The gel prepared from 40% by weight of a 50:50 lactic
18 acid:glycolic polymer and 60% by weight triacetin is thick and thus difficult to
19 inject but shows little burst (less than 2% of the beneficial agent is delivered in the
20 first eight days). The gel prepared from 40% by weight of a 50:50 lactic
21 acid:glycolic polymer and 60% by weight N-methyl-2-pyrrolidone is thin and
22 injectable but shows a large burst (greater than 70% of the beneficial agent is
23 delivered in the first eight days). The gel prepared from 27% by weight of a 50:50
24 lactic acid:glycolic polymer, 40% by weight triacetin and 33% by weight of a 10%
25 ethanol, 90% isotonic saline solution is thin and injectable and shows little burst
26 (less than 10% of the beneficial agent is delivered in the first eight days). In each
27 case, lysozyme is the beneficial agent and comprises 20% by weight of the
28 combined beneficial agent, polymer and solvent formulation.

1 emulsifying agent and (c) beneficial agent. Prior to use the beneficial agent is mixed
2 with the emulsifying agent, and that solution or suspension is mixed with the
3 polymer/solvent mixture to prepare the injectable depot implant for use.

4 The emulsifying agent is present in an amount ranging from about 5 to about
5 80%, preferably from about 20 to about 60% and often 30 to 50% by weight based
6 on the amount of the injectable depot gel composition, that is the combined amounts
7 of polymer, solvent, emulsifying agent and beneficial agent. Illustrative
8 emulsifying agents are water, alcohols, polyols, esters, carboxylic acids, ketones,
9 aldehydes and mixtures thereof. Preferred emulsifying agents are alcohols,
10 propylene glycol, ethylene glycol, glycerol, water, and solutions and mixtures
11 thereof. Especially preferred are water, ethanol, and isopropyl alcohol and
12 solutions and mixtures thereof. The type of emulsifying agent affects the size of the
13 dispersed droplets. For instance, ethanol will provide droplets that have average
14 diameters that can be on the order of ten times larger than the droplets obtained with
15 an isotonic saline solution containing 0.9% by weight of sodium chloride at 21°C.

16 While normally no other components are present in the composition, to the
17 extent that conventional optional ingredients are desired, such as polyethylene
18 glycol, hydroscopic agents, stabilizing agents and others, they are used in an
19 amount that does not substantially affect the advantageous results which can be
20 attained in accordance with the present invention.

21 To illustrate various aspects of the invention further, Figure 3 shows the
22 viscosities at different shear rates using water alone and an aqueous mixture
23 containing 10% by volume of ethanol at a weight ratio of 2:1 (gel:emulsifying
24 agent) using a viscous gel formed from 50% by weight of a 50:50 lactic
25 acid:glycolic acid copolymer and 50% by weight of triacetin compared to the
26 viscosities of the viscous gel without emulsifying agent.

27 It is to be understood that the emulsifying agent of the present invention does
28 not constitute a mere diluent that reduces viscosity by simply decreasing the
29 concentration of the components of the composition. The use of conventional

1 solution, as an emulsifying agent, in the amount used in Example 1. The
2 emulsifying agent-lysozyme solution is mixed with the amount of gel material used
3 in Example 1 to form an injectable depot gel composition. The fabricated injectable
4 depot gel composition is suitable for injection into an animal.

5 In accordance with various aspects of the present invention, one or more
6 significant advantages can be obtained. More specifically, using simple processing
7 steps, one can obtain a depot gel composition that can be injected into place in an
8 animal without surgery using a low dispensing force through standard needles.
9 Once in place, the composition will quickly return to its original viscosity and may
10 exhibit rapid hardening so as to substantially avoid a burst effect and provide the
11 desired beneficial agent release profile. Furthermore, once the beneficial agent has
12 been fully administered, there is no need to remove the composition since it is fully
13 biodegradable. As a still further advantage, the present invention avoids the use of
14 microparticle or microcapsulation techniques which can degrade certain beneficial
15 agents, like peptide and nucleic acid-based drugs and which microparticles and
16 microcapsules maybe difficult to remove from the environment of use. Since the
17 viscous gel is formed without the need for water, temperature extremes, or other
18 solvents, suspended particles of beneficial agent remain dry and in their original
19 configuration, which contributes to the stability of thereof. Further, since a mass is
20 formed, the injectable depot gel composition may be retrieved from the environment
21 of use if desired.

22 The above-described exemplary embodiments are intended to be illustrative
23 in all respects, rather than restrictive, of the present invention. Thus the present
24 invention is capable of many variations in detailed implementation that can be
25 derived from the description contained herein by a person skilled in the art. All
26 such variations and modifications are considered to be within the scope and spirit of
27 the present invention as defined by the following claims.

1 4. The injectable depot gel composition of claim 3 wherein the lactic acid-
2 based polymer has a monomer ratio of lactic acid to glycolic acid in the range of
3 100:0 to about 15:85.

4

5 5. The injectable depot gel composition of claim 3 wherein the lactic acid-
6 based polymer has a number average molecular weight of from 1,000 to 120,000.

7

8 6. The injectable depot gel composition of claim 1 wherein the solvent that
9 can dissolve the biocompatible polymer to form a viscous gel is selected from the
10 group consisting of triacetin, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol
11 formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide,
12 dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethysulfoxide, oleic acid,
13 and 1-dodecylazacyclo-heptan-2-one and mixtures thereof.

14

15 7. The injectable depot gel composition of claim 1 wherein the solvent is
16 selected from the group consisting of triacetin and N-methyl-2-pyrrolidone, and
17 mixtures thereof.

18

19 8. The injectable depot gel composition of claim 1 wherein the solvent is
20 triacetin.

21

1
2 16. The injectable depot gel composition of claim 1 wherein the beneficial
3 agent is present in an amount of from 1 to 50% by weight of the combined amounts
4 of the polymer, the solvent and the beneficial agent.

5
6 17. The injectable depot gel composition of claim 1 wherein the beneficial
7 agent is in the form of particles dispersed or dissolved in the viscous gel.

8
9 18. The injectable depot gel composition of claim 17 wherein the beneficial
10 agent is in the form of particles having an average particle size of from 0.1 to 100
11 microns.

12
13 19. The injectable depot gel composition of claim 1 wherein the emulsifying
14 agent is selected from the group consisting of water, alcohols, polyols, esters,
15 carboxylic acids, ketones, aldehydes and mixtures thereof.

16
17 20. The injectable depot gel composition of claim 1 wherein the emulsifying
18 agent is selected from the group consisting of alcohols, propylene glycol, ethylene
19 glycol, glycerol, water and solutions and mixtures thereof.

20
21 21. The injectable depot gel composition of claim 1 wherein the emulsifying
22 agent is selected from the group consisting of ethanol, isopropyl alcohol, water,
23 solutions thereof, and mixtures thereof.

24

1 C) mixing the beneficial agent containing emulsifying agent with the viscous
2 gel, said beneficial agent containing emulsifying agent forming a dispersed droplet
3 phase in the viscous gel to provide the injectable depot composition.

4

5 26. An injectable depot gel composition comprising:

6 A) a biocompatible polymer;

7 B) a solvent that dissolves the polymer and forms a viscous gel; and

8 C) an emulsifying agent in the form of a dispersed droplet phase in the
9 viscous gel.

10

11 27. A kit adapted to provide an injectable depot composition comprising as
12 kit components: (a) a biocompatible polymer and a solvent that dissolves the
13 polymer and forms a viscous gel; (b) emulsifying agent; and (c) beneficial agent.

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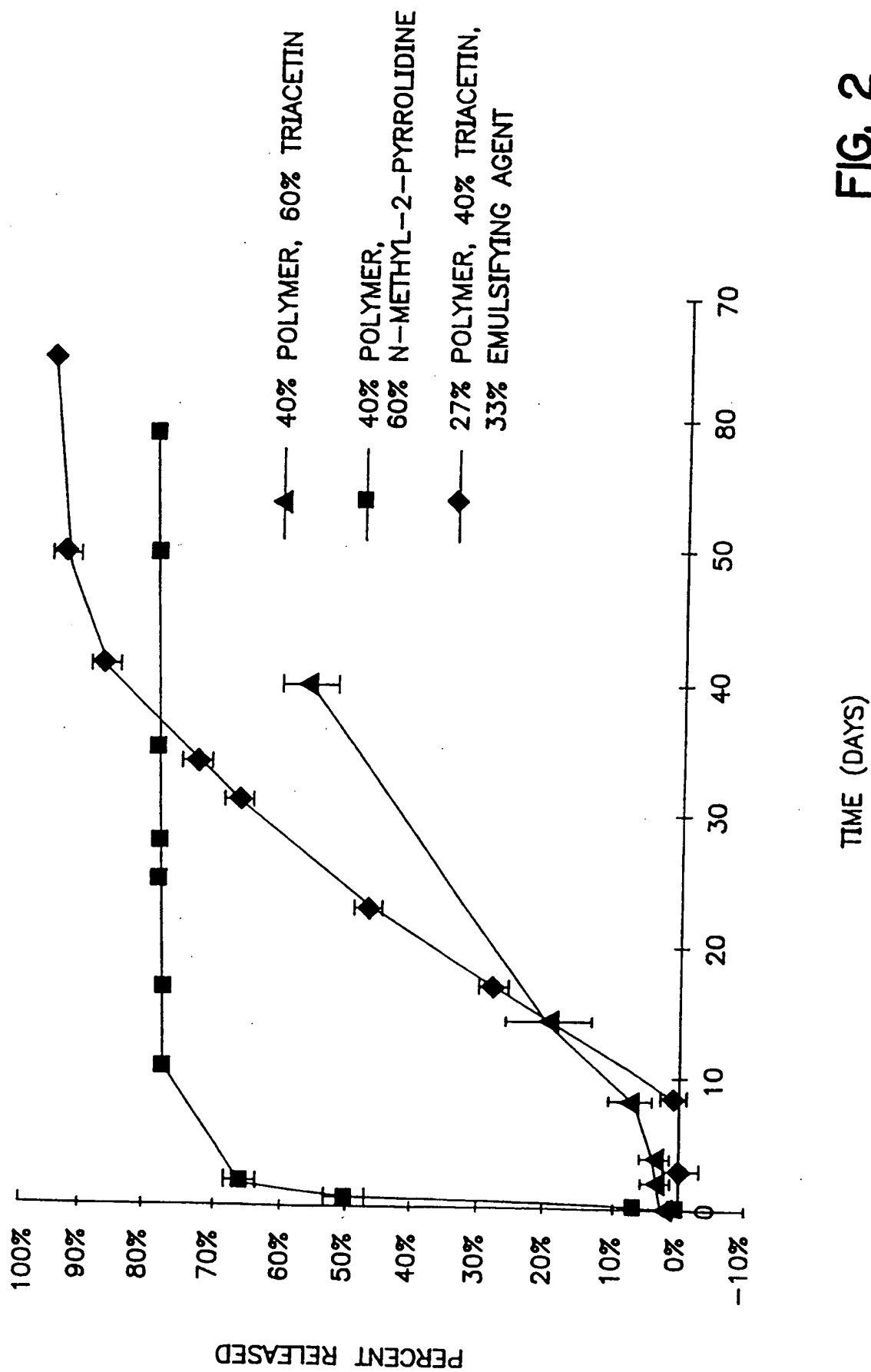


FIG. 2